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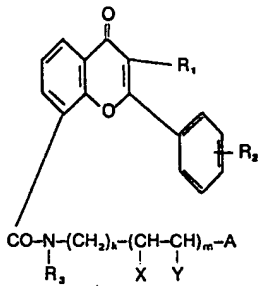
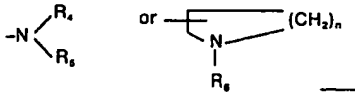
(54) **N-substituted flavone-8-carboxamides.**

(57) Derivatives of N-substituted flavone-8-carboxamides represented by general formula (I)



wherein R_1 represents a hydrogen atom, a methyl group or an ethyl group, R_2 represents a hydrogen atom, a lower alkyl group, a lower alkoxyl group, a halogen atom or a nitro group, R_3 represents a hydrogen atom or a lower alkyl group, k represents 0, 1, 2, or 3, m represents 0 or 1, X and Y, which must be different, represents a hydrogen atom or a methyl group, A represents an amino group having the



wherein, R_4 and R_5, which may be the same or different, represent a lower alkyl group or a cyclic amino group together with the nitrogen atom and with or without an oxygen atom, R_6 represents a lower alkyl group and n represents 2 or 3, are disclosed as well as pharmaceutical compositions thereof and method of treating therewith.

The N-substituted flavone-8-carboxamides derivatives are useful as agents for treatment of dysurea.

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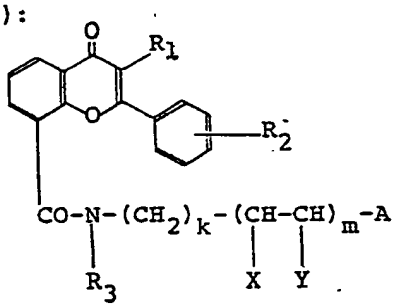
N-SUBSTITUTED FLAVONE-8-CARBOXAMIDES

BACKGROUND OF THE INVENTION

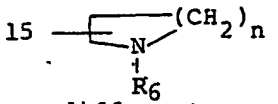
FIELD OF THE INVENTION

The present invention relates to novel derivatives of N-substituted flavone-8-carboxamide represented by the formula (I):



(I)

wherein R_1 represents a hydrogen atom, a methyl group or an ethyl group; R_2 represents a hydrogen atom, a lower alkyl group, a lower alkoxyl group, a halogen atom or a nitro group; R_3 represents a hydrogen atom or a lower alkyl group; k represents 0,1,2, or 3; m represents 0 or 1, X and Y, which must be different, represent a hydrogen atom or a methyl group; A represents an amino group having the $-N\begin{matrix}R_4\\R_5\end{matrix}$ or



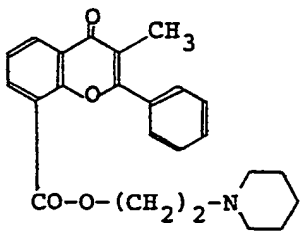
wherein, R_4 and R_5, which may be the same or different, represent a lower alkyl group or a cyclic amino group together with the nitrogen atom and with or without an oxygen atom; R_6 represents a lower alkyl group and n re-

presents 2 or 3; which have an excellent effect for removing the difficulties on urination (dysuria), non-toxic pharmaceutically acceptable salts thereof and process for preparation thereof.

The present invention also relates to pharmaceutical compositions containing the derivatives of the formula (I) and further to a method of treating a patient with disease therewith.

DESCRIPTION OF THE PRIOR ART

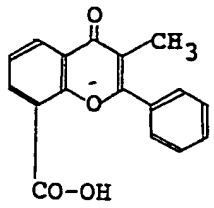
As no therapeutical agent having a specific effect for removing the hinderances in micturition was known, it has been used hetherto to eliminate the difficulties on urination only antispasmodics or tranquilizers. Recently it is known that Flavoxate of the chemical formula(II);



(II)

possesses an activity for treatment of dysuria in practice (Merck Index, 9th Eddition, 4012; U.S.Patent 2,921,070). The compound of the prior art is, however, unsatisfactory for

clinical use because of its poor effect and lower stability. The compound administrated per os is hydrolyzed in digestric tract to an less active free carboxylic acid having the formula (III);



(III)

SUMMARY OF THE INVENTION

An object of the present invention is to provide a satisfactory therapeutic agent having high order of an activity for removing the hindrances in micturition with sufficient stability, so that useful as a medicine with extremely favorable results.

A further object of the present invention is to provide a therapeutic composition containing compounds of formula (I) and a method of treating a patient with disease therewith.

DETAILED DESCRIPTION OF THE INVENTION

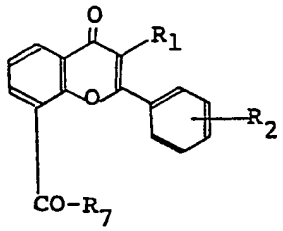
In more detail, the lower alkyl group for R_2 and R_3 in the formula (I) represent, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tert-butyl group; the

lower alkoxyl group for R_2 represents, for example, methoxyl, ethoxyl, propoxyl, isopropoxyl or butoxyl group, and halogen atom represents, for example, fluorine, chlorine or bromine atom. The amino group of the formula $-N\begin{matrix}R_4\\R_5\end{matrix}$ in the formula (I) represents, for example, dimethylamino, diethylamino, dipropylamino, dibutylamino, methylbutylamino, pyrrolidino, piperidino, morpholino group, and the amino group of the formula $-E-N(CH_2)_n$ (R_6) represents, for example, 1-methyl-2-pyrrolidyl, 1-ethyl-2-pyrrolidyl, 1-butyl-2-pyrrolidyl, 1-methyl-3-pyrrolidyl, 1-ethyl-3-pyrrolidyl, 1-butyl-3--pyrrolidyl, 1-methyl-2-piperidyl, 1-ethyl-2-piperidyl, 1-butyl-2-piperidyl, 1-methyl-3-piperidyl, 1-ethyl-3-piperidyl, 1-butyl-3-piperidyl, 1-methyl-4-piperidyl, 1-ethyl-4-piperidyl, 1-butyl-4-piperidyl group. If necessary, the compounds of the present invention represented by formula (I) can be converted into pharmaceutically acceptable acid addition salts in a conventional manner and the acid addition salts can be converted into the free base too.

The pharmaceutically acceptable acid addition salts are, for example, the inorganic acid addition salts such as hydrochloride, hydrobromide , hydroiodide, nitrate, sulfate or phosphate or the organic acid addition salts such as acetate, maleate, fumarate, citrate, oxalate or tartarate.

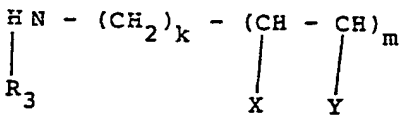
The novel derivatives of N-substituted flavone-8-

carboxamide of the formula (I) can be prepared by reaction of a derivative of flavone-8-carboxylic acid of the formula (IV);



(IV)

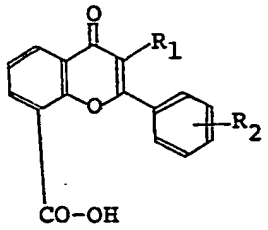
wherein R_1 and R_2 have the same meanings as defined above, R_7 represents a hydroxyl group, a halogen atom, a group of formula $O-R_8$ or $O-CO-OR_9$, wherein each of R_8 and R_9 represent a lower alkyl group, with a diamine derivative of the formula (V);



(V),

wherein R_3, k, m, X, Y and A have the same meanings as defined above.

According to the first embodyment of the preparation of the compounds of the present invention, a derivative of flavone-8-carboxylic acid of the formula (IV-1);



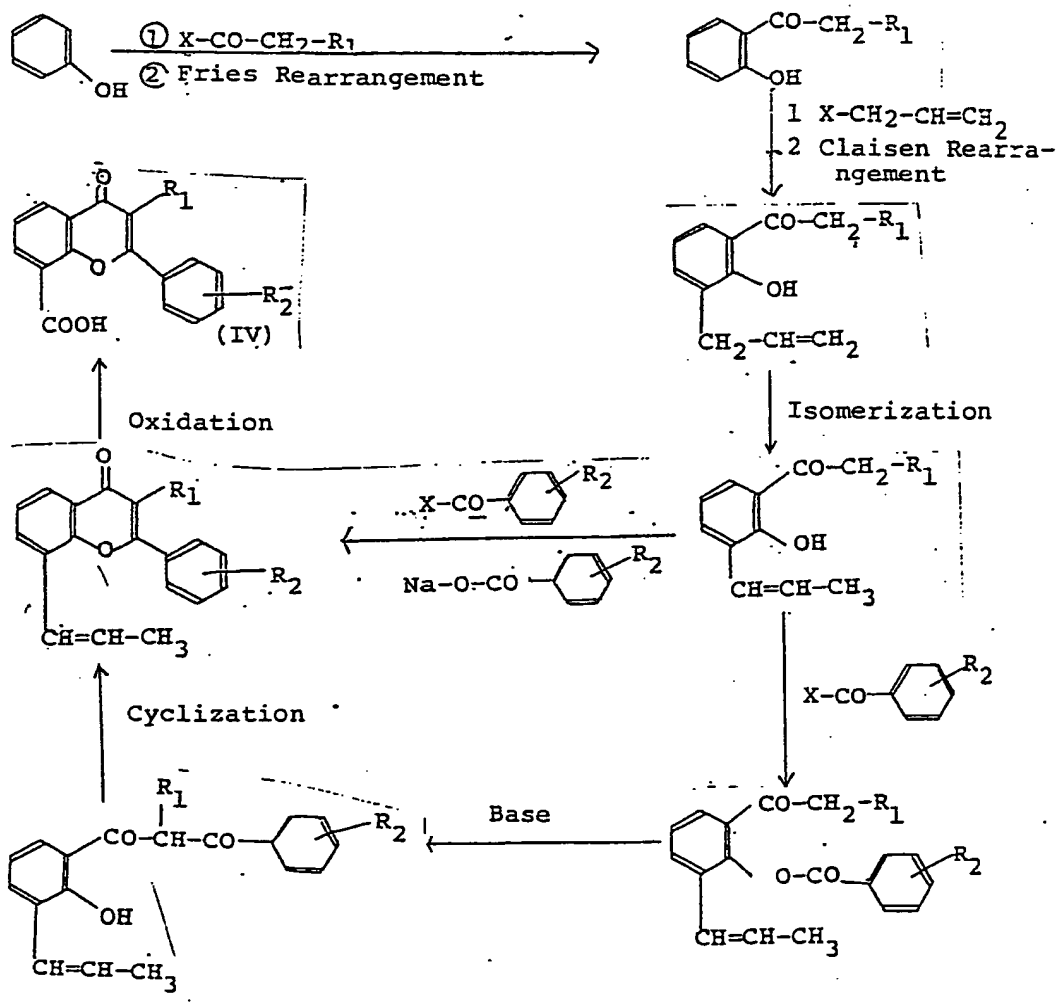
(IV-1)

wherein R_1 and R_2 having the same meanings as defined above, has been reacted with a diamine derivative of the formula (V) in inert organic solvents in the presence of a condensing agent. The condensing agent to be used in the preparation of the present invention is, for example, carbodiimides such as N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholino-ethylcarbodiimide or N-cyclohexyl-N'-(4-diethylamino-cyclohexyl)carbodiimide, phosphorus halogenides such as phosphorus trichloride, phosphorus oxychloride, diethyl-chlorophosphite, o-phenylenechlorophosphite, ethylene-dichlorophosphite or phosphoric anhydride.

The inert organic solvents to be used in the present invention are, for example, acetone, dioxane, acetonitrile, chloroform, methylene chloride or tetrahydrofuran.

The reaction is performed at -10°C to a boiling point of the solvent used, (e.g., reflux temperature), preferably at a room temperature.

The derivatives of flavone-8-carboxylic acid of formula (IV-1) wherein R_2 is a hydrogen atom as a starting material of the preparation of the present invention are known compounds and can be prepared in a conventional manner (Chemische Berichte 99, 1962 (1966)). The flavone-8-carboxylic acid of the formula (IV-1), wherein R_2 is a lower alkyl group, a lower alkoxyl group, a halogen atom or a nitro group is new compound and can be prepared as following schemes.

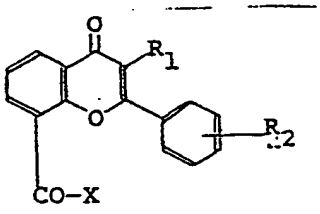


(wherein R_1 has the same meanings as defined above, R_2 represents a lower alkyl group, a lower alkoxyl group, a halogen atom or a nitro group and X represents a halogen atom.)

Diamine derivatives of the formula (V), as a starting material are known compounds and can be prepared by a conventional manner, for example, in accordance with the following literatures:

Journal of the American Chemical Society 72, 3004 (1950); 68, 100 (1946); 68, 1607 (1946); 66, 725 (1944); 65, 2012 (1943); Helvetica Chimica Acta 26, 1172 (1943); Shionogi Kenkyusho Nempo 10, 1, (1960); Yakugaku Zasshi 62, 224 (1942); 68, 221 (1948); 75, 153 (1955); 81, 149 (1961), Japanese Patent Publication 14097 (1972).

According to the second embodiment of the preparation of the compounds of the present invention a derivative of flavone-8-carboxylic acid halogenide of the formula (IV-2);



(IV-2)

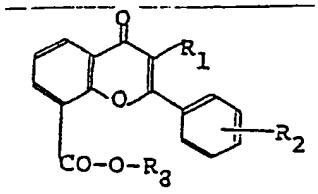
wherein R_1 and R_2 have the same meanings as defined above, X represents a halogen atom, has been reacted with a diamine derivative of the formula (V) in an inert organic solvent.

As the inert organic solvent to be used in the preparation of the present invention can be used any solvents, which do not inhibit the reaction, for example, acetone, ether, tetrahydrofuran, dioxane, benzene, toluene or chloroform.

The reaction is performed at a room temperature to a reflux temperature of the solvent used, preferably at a room temperature.

The flavone-8-carboxylic acid halogenide derivative of the formula (IV-2) as a starting material of the preparation of this invention can be prepared from flavone-8-carboxylic acid derivatives of the formula (IV-1) in accordance with the conventional manner at the time of the usage.

According to the third embodiment of the preparation of the compounds of the present invention, an ester derivative of flavone-8-carboxylic acid of the formula (IV-3);



(IV-3)

wherein R_1 and R_2 have the same meanings as defined above, and R_8 represents a lower alkyl group, has been reacted with a diamine derivative of the formula (V) in an inert organic solvent.

As the inert organic solvent for preparation of the present invention can be used any solvents, which do not inhibit the reaction, for example, lower alcohols such as methanol or ethanol, aromatic hydrocarbones, such as, benzene, xylene or toluene, ethers such as, ether, dioxane or tetrahydrofuran, or aprotic polar solvents such as, dimethylformamide, dimethylsulfoxide or hexamethylphosphoric triamide.

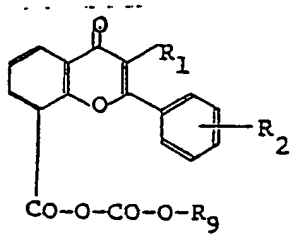
The reaction is performed at a room temperature to a reflux temperature of the solvent used, preferably at the reflux temperature of the solvent used.

The ester derivative of flavone-8-carboxylic acid of the formula (IV-3) as a starting material of the preparation of the invention are novel compounds excepting the compounds of the formula (IV-3), wherein R_2 represents a hydrogen atom and R_8 represents methyl or ethyl group (Chemische Berichte 99, 1962 (1966); DOS 2051269) and can be prepared by the reaction of a flavone-8-carboxylic acid halogenide of the formula (IV-2) with a lower alkanol of the formula (VI)

$$R_8\text{-OH} \qquad \text{(VI)}$$

wherein R_8 has the same meanings as defined above.

According to the fourth embodiment of the preparation of the present invention the mixed anhydride derivative of the flavone-8-carboxylic acid of the formula (IV-4)



(IV-4)

wherein R_1 and R_2 have the same meanings as defined above and R_9 represents a lower alkyl group, has been reacted with a diamine derivative of the formula (V) in an inert organic solvent.

As the inert organic solvent for preparation of the present invention can be used any solvents, which do not inhibit the reaction, for example, ketones, such as acetone, an aromatic hydrocarbones, such as benzene or toluene, ethers, such as ether, dioxane or tetrahydrofuran, halogenated hydrocarbons, such as, chloroform or methylene chloride, or aprotic polar solvents, such as dimethylformamide or hexamethylphosphoric triamide.

The reaction is performed at -10° C to a reflux

temperature of the solvent used, preferably at or a bout room temperature. The mixed anhydride derivative of flavone-8-carboxylic acid of the formula (IV-4) as a starting material can be prepared by the reaction of an alkyl halogenbcarbonate of the formula (VII)

$$X - CO - O - R_9 \qquad (VII)$$

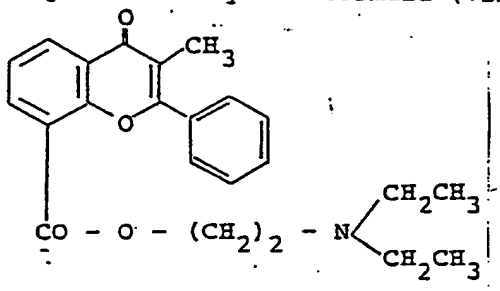
wherein R_9 has the same meanings as defined above, and X represents a halogen atom, with the flavone-8-carboxylic acid derivative of the formula (IV-1) in the presence of triethylamine in a conventional manner.

The thus prepared N-substituted flavone-8-carboxamide derivatives represented by formula (I) and pharmaceutically acceptable acid addition salts thereof exhibit an effect for removing the hindrance in micturation, that is supression of urinary reflex and contraction of urinary bladder etc. and are extremely useful as medicament for removing the dysurea, such as pollakiuria caused by neuropathic pollakiuria, chronic prostatitis and chronic cystitis etc.

As an example showing effective activity for removing the hinderance in micturition of the present compounds, supression of urinary reflex is shown in Table I, and the excellent stability thereof is shown in Table II.

As reference drugs, three medicaments, flavoxate

represented by formula (II), whcih is on the market, an ester derivative (a compound according to U.S. Patent 2,921,070, Example 2) represented by the formula (VIII);

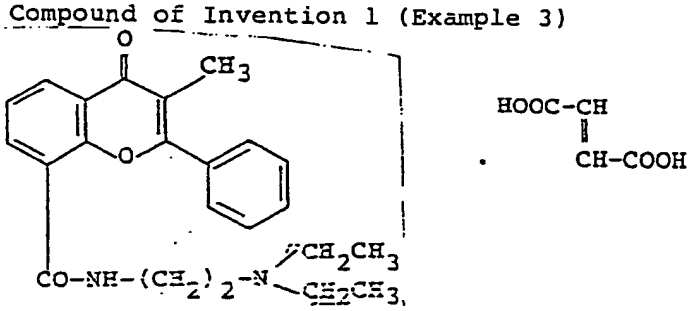


(VIII)

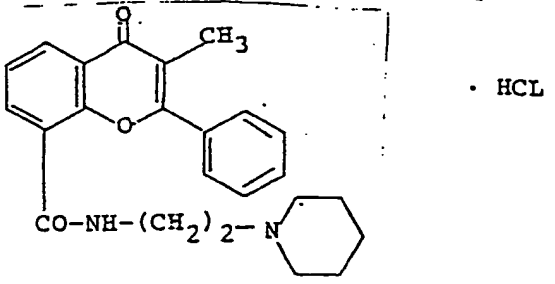
which possess a structure similar to that of the present compounds, and free carboxylic acid represented by formula (III) and prepared by hydrolysis thereof, are used.

(Test Compounds)

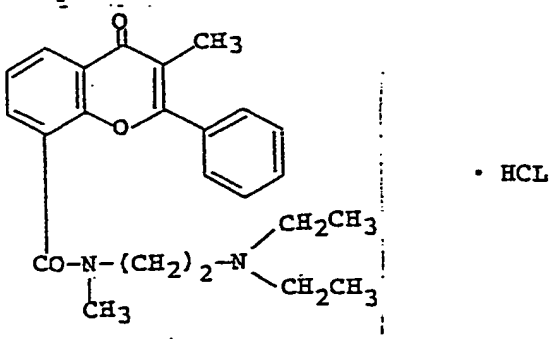
- Compound of Invention 1 (Example 3)



- Compound of Invention 2 (Example 14)

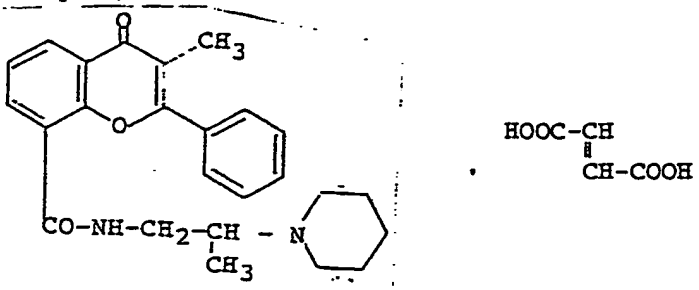


o Compound of Invention 3 (Example 7)



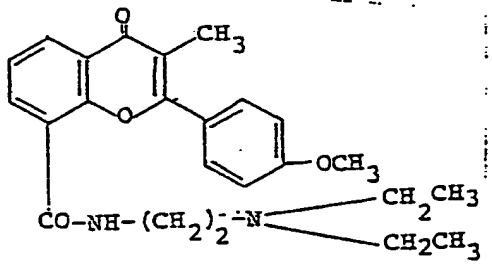
• HCL

o Compound of Invention 4 (Example 29)

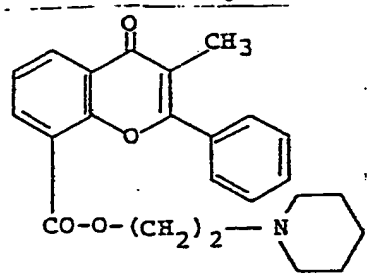


HOOC-CH
||
CH-COOH

o Compound of Invention 5 (Example 36)

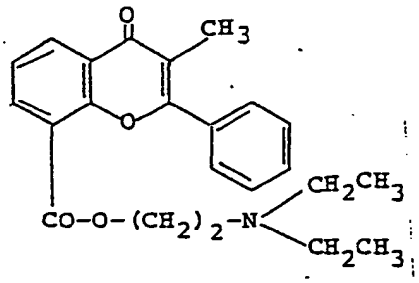


o Reference Drug 1 (flavoxate hydrochloride)



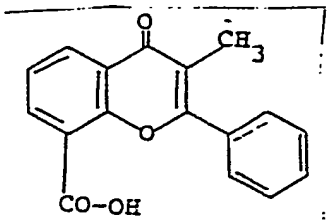
• HCL

o Reference Drug 2



· HCL

o Reference Drug 3



(1) Supression of urinary reflex

(Experiment)

According to the method of kaseda et al (Rinsho Seiri, 5, 540 (1975)), male Wister rats weighing approximately 300 g and fasted for 15 to 20 hours prior to experiments were anesthetized by intraperitoneal injection of 500 mg/Kg of urethane and 50 mg/Kg of α-chloralose, and fixed to a supine position. Then the lower abdomen was opened through a midline incision to expose the bladder, and a balloon (1.5 to 2.0 cm^3) was inserted into the urinary bladder via small incision in the base thereof. The change of inner pressure

is recorded via pressure transducer. The urinary reflex was induced by elevating the inner pressure to 10 to 20 cm H_2O. Urine was excreted from the incision of the bladder, where balloon was inserted.

The test compounds were given through polyethylene tube inserted into duodenum via an incision in the fundus.

Mean value of contraction according to the urinary reflex appeared during ten minutes before the administration of the compounds, and at 15, 30, 45 and 60 minutes thereafter have been investigated for the judgement of the effect of the present compounds. The mean value suppressed by more than 50% compared as the initial value has been estimated as effect. ID_{50} (50% effective dose) was obtained by up and down method.

The result was shown in Table 1.

Table 1: Supression of Urinary Reflex

Test Compounds	ID_{50} (mg/Kg)	Ratio of Effect*
Compound 1	36.7	7.42
Compound 2	26.8	10.16
Compound 3	46.7	5.83
Compound 4	46.7	5.83
Compound 5	93.3	2.92
Reference 1	272.3	1.00
Reference 2	325.1	0.84
Reference 3	307.6	0.89

* The Effect of Reference is defined as 1.00

The compounds of the present invention had about 3 to 10 times more potent effect of supressing urinary reflex than Reference drug 1 (flavoxate), which was on the market, as well as than Reference drug 2, which possess the structure similar to the compounds of the present invention.

(2) Stability in acidic medium (corresponding to artificial small intestinal juice)

(Experiment)

After sacrificing male Wister rats (approximatly weighing 300 g), small intestine was taken out and small

intestinal mucous membrane was scraped off, and 20 ml of 0.1 M phosphate buffer (pH 6.00) were added per 0.5 g of small intestinal mucous membrane (wet weight) to give 2.5% of homogenate.

Test compound was dissolved in the homogenate to give definite concentration (50 µM) under shaking of the obtained mixture at 37 °C. sampling was carried out from time to time, and the content of each compound was quantitatively measured by analyzing peak height of each compound by a reversed-phase high performance liquid chromatography. The half-life time of each compound in acidic medium (corresponding to artificial small intestinal juice, pH 6.0) was measured from a graph indicating content change of each compound against time.

Table 2: Half-life Time (T 1/2)

Compounds	T 1/2 (hr)	Ratio of Effect*
Compound 1	650.3	1066.1
Compound 2	290.0	475.4
Compound 3	153.8	252.1
Compound 4	778.9	1276.9
Compound 5	718.2	1177.4
Reference 1	0.61	1.0
Reference 2	1.39	2.3

* Stability of reference 1 is difined as 1.0

The compounds of the present invention and flavoxate (Reference 1) should absorbed, after p.o. administration at small intestine to show medical effect. Therefore the stability of the compounds against the hydrolyzation according to the nonspecific esterase contained in small intestinal mucous membrane is very important.

The stability of the compounds of the present invention is 110 to 1200 times stronger than References 1 and 2 and excellent as medicament for clinical use.

A compound of the present invention represented by general formula (I) can be administered per os, e.g., in the form of pills or tablets, in which it may be present together with the usual pharmaceutical carriers, conventionally by compounding the compounds of this invention together with a customary carrier or adjuvant, such as talc, magnesium stearate, starch, lactose, gelatin, any of numerous gums, and the like. Thus, in their most advantageous form, the compositions of this invention will contain a non-toxic pharmaceutical carrier in addition to the active ingredient of the present invention. Exemplary solid carriers are lactose, magnesium stearate, calcium stearate, starch terra alba, dicalcium acacia, or the like. Representative liquid carriers are peanut oil, sesame oil, olive oil, water, or the like. The active agents of this invention can be conveni-

ently administered in such compositions containing active ingredient so as to eventually be within the dosage range illustrated hereafter. Thus, a wide variety of pharmaceutical forms suitable for many modes of administration and dosages may be employed. For oral administration, the active ingredient and pharmaceutical forms suitable for many modes of administration and dosages may be employed. For oral administration, the active ingredient and pharmaceutical carrier may, for example, take the form of a granule, pill, tablet, lozenge, elixir, syrup, or other liquid suspension or emulsion, whereas, for parenteral administration, the composition may be in the form of a sterile solution.

The method of using the compounds of this invention comprises internally or externally administering a compound of this invention, preferable orally or parenterally and preferably admixed with the pharmaceutical carrier, for example, in the form of any of the above compositions, or filled into a capsule, to alleviate conditions to be treated and symptoms thereof in a living animal body. Illustratively, it may be used in an amount of about 50 to about 300 mg. per unit dose, preferably 100 to 200 mg. and 3 times per day for an oral dose and for adult while parenteral dosages are usually less and ordinarily about one-half of the oral

dose.

The unit dose is preferably given a suitable number of times daily, typically three times. The daily dose may vary depending upon the number of times given. Naturally, a suitable clinical dose must be adjusted in accordance with the conditon, age, and weight of the patient, and it goes without saying that the enhanced activities of the compounds of the invention, together with their reduced side effects, also make them suitable for wide variations, and this invention therefore should not be limited by the exact ranges stated. The exact dosage, both unit dosage and daily dosage, will of course have to be determined according to established medical principles.

The following examples are given by illustration only and are not to be construed as limitations of this invention, many variations of which are possible without departing from the scope and spirit thereof.

Example 1

N-[2-(N , N'-dimethylamino)]ethyl -3-methylblavone-8-carboxyamide:

To a solution of 1.53 g of 3-methyflavone-8-carboxylic acid chloride in 60 ml of benzen were added 0.41 g of N, N-dimethylethylenediamine and solution was refluxed for 2 hours. After cooling, the reaction mixture was extracted with aqueous HCl solution. The water layer was made alkaline

with potassium carbonate, and extracted with chloroform. The extract was washed with water, dried, and then evaporated. To the residue, ether was added. The precipitate was filtered to give 0.76 g of colorless crystal, m.p. 133 to 135.5°C. According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as colorless needles, m.p. 168 to 170.5°C.

Elemental analysis for $C_{21}H_{22}N_2O_3 \cdot O_4H_4O_4$

	C	H	N
Calcd. (%)	64.37	5.62	6.01
Found (%)	64.48	5.70	5.96

Example 2

N-[2-(N', N'-Diethylamino) ethyl] flavone-8-carbox amide:

To a solution of 3.20 g of flavone-8-carboxylic acid chloride in 100 ml of benzene were added 1.19 g of N, N-diethylethylenediamine and the solution was refluxed for one hour. After cooling, the precipitate was filtered and dissolved in water. The solution was made alkaline with potassium carbonate, and extracted with chloroform. The extract was washed with water and dried, and then evaporated. To the residue, ether was added. The precipitation was filtered to give 2.25 g of colorless crystals, m.p. 169 to 171°C. According to a conventional manner, the compound was

changed to fumarate, which was recrystallized from ethanol as colorless needle, m.p. 179.5 to 180.5°C.

Elemental analysis for $C_{22}H_{24}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd. (%)	64.99	5.87	5.83
Found (%)	65.06	5.96	5.78

Example 3

N-[2-(N', N'-Diethylamino) ethyl]-3-methylflavone-8-carbox amide:

a) To a solution of 38.72 g of 3-methyflavone-8-carboxylic acid chloride in 500 ml of benzene were added 11.30 g of N, N-diethylethylenediamine and the solution was refluxed for o.5 hours. The reaction mixture was treated by the same manner as that described for Example 2 to give 34.3 g of colorless crystals, which recrystalized from isopropyl ether as a colorless needles, m.p. 105.5 to 108.5°C.

Elemental analysis for $C_{23}H_{26}N_2O_3$

	C	H	N
Calcd. (%)	72.99	6.92	7.40
Found (%)	72.79	7.16	7.23

According to a conventional manner, the compound was changed to formarate, which was recrystallized from ethanol as cloreless plates, m. p. 172.5 to 174.5 °C.

Elemental analysis for $C_{23}H_{26}N_2O_3 \cdot C_4H_4O_4$

		C	H	N
Calcd.	(%)	65.58	6.11	5.66
found	(%)	65.35	6.08	5.77

b) To a solution of 1.00 g of ethyl-3-methylflavone-8-carboxylate in 10 ml of ethanol were added 0.55ml of N, N-diethylethylenediamine and the solution was refluxed for 25.5 hours. The solution was evaporated and the residue was dissolved in aqueous HCl solution was washed with ethyl acetate.. The water layer was made alkaline with potassium carbonate and extracted with ethyl acetate. The extract was washed with water, dried and evaporated. To the residue was added isoprophyl ether and the precipitate was filtered to give 0.25 g of pale yellow crystals, which were recrystallized from isopropyl ether as colorless needles, m.p. 105.5 - 108°C. This compound is identical with the product obtained in Example 3-a) in NMR and IR spectra, and mixed m. p..

c) To an ice-cooling suspension of 1.00 g of 3-methylflavone-8-carboxylic acid in 20 ml of methylene chrolide were added 0.88 g of N, N-dicyclohexylcarbodiimide with stirring, and after 10 minutes added 0.50 ml of N, N-diethylethylenediamine. The mixture was stirred for 1 hour under ice-cooling and then at room temperature for 17 hours.

The precipitate was filtrated off and the filtrate was evaporated. The residue was treated by the same manner as that described for Example 3-b) to give 0.45 g of colorless crystals, which were recrystallized from isopropyl ether as colorless needle, m. p. 105.5 - 108 °C. This compound is identical with the product obtained in Example 3-a) in NMR and IR spectra, and mixed m. p..

d) To an ice-cooling solution of 1.00 g of 3-methylflavone-8-carboxylic and 0.50 ml of tryethylamine in 21.5 ml of dry tetrahydrofuran was added a solution of 0.38 ml of ethyl chlorocarbonate in 1 ml of dry tetrahydrofuran and after one hour added a solution of 0.5 ml of N,N-diethyl-ethylenediamine in 1.5 ml of dry tetrahydrofuran. The mixture was stirred for 1.5 hours under ice-cooling and then at room temperature for 16 hours. The precipitate was filtrated off and the filtrate was evaporated. The residue was treated by the same manner as that described for Example 3-b) to give 0.94 g of colorless crystals, which were recrystallizated from isopropyl ether as colorless needles, m.p. 105.5 to 108°C. This compound was identified with the product obtained in Example 3-a) in NMR and IR spectra, and mexed m. p..

e) To a solution of 1.00 ml of N, N-diethyl-ethylenediamine in 10 ml of pyridine was added a solution of

0.31 ml of phosphorus trichloride in 2 ml of pyridine under ice-cooling, and the mixture was stirred for 5 minutes under ice-cooling and 1 hour at room temperature. Then to the mixture were added 1.00 g of 3-ethylflavone-8-carboxylic acid and the mixture was stirred for 4.5 hours at 90 to 100°C. The mixture was evaporated and the residue was treated by the same manner as that described for Example 3-b) to give 0.65 g of colorless crystals, which were recrystallizated from isopropyl ether as colorless needles, m.p. 105.5 to 108°C. This compound is identical with the product obtained in Example 3-a) in NMR and IR spectra, and mixed m. p..

Example 4

N-[N',N'-Diethylamino) ethyl]-3-ethylflavone-8-carboxamide:

To a solution of 3.15 g of 3-ethylflavone-8-carboxylic acid chloride in 100 ml of benzene were added 1.06 g of N,N-diethylethylenediamine and the solution was refluxed for 10 minutes. After cooling, the precipitate was filtered and recrystalliqed from ethanol to give 3.15 g of hydrochloride as colorless needles, m.p. 178 - 180.5 °C.

Elemental analysis for $C_{24}H_{28}N_2O_3 \cdot HCl$

		C	H	N
Calcd.	(%)	67.20	6.81	6.53
Found	(%)	67.38	6.97	6.43

Example 5

N-[3-(N', N'-Diethylamino) propyl]-3-methylflavone-8-carbox - amide:

To a solution of 1.51 g of 3-methylflavone-8-carboxylic acid chloride in 70 ml of benzene were added 0.60 g of N, N-diethyl-1,3-propanediamine and the solution was stirred at room temperature for 0.5 hours. The reaction mixture was extracted with aqueous HCl solution. The water layer was made alkaline with potassium carbonate, and extracted with ethyl acetate. The extract was washed with water, dried, and then evaporated. To the residue, ether was added. The precipitation was filtered to give 0.92 g of pale brown crystals, which were recrystallized from isopropyl ether as colorless needles, m.p. 103 to 104.5°C.

Elemental analysis for $C_{24}H_{28}N_2O_3$

		C	H	N
Calcd.	(%)	73.44	7.19	7.14
Found	(%)	73.39	7.29	7.00

Example 6

N-[3-(N', N'-Dipropylamino)propyl]-3-ethylflavone-8-carbox - amide:

To a solution of 1.60 g of 3-ethylflavone-8-carboxylic acid chloride in 60 ml of benzene were added 0.73 g of N, N-dipropyl-1,3-propanediamine and the solution was refluxed

for 1.5 hours. The solution mixture was treated by the same manner as that described for Example 2, to give 1.25 g of colorless crystals, which were recrystallized from isopropyl ether as colorless needles, m.p. 105.5 to 106°C.

Elemental analysis for $C_{27}H_{34}N_2O_3$

		C	H	N
Calcd.	(%)	74.62	7.89	6.45
Found	(%)	74.75	8.22	6.32

Example 7

N-[2-(N', N'-Diethylamino) ethyl]-N-methyl-3-methylflavone-8-carbox amide:

To a solution of 3.30 g of 3-methylflavone-8-carboxylic acid chloride in 90 ml of benzene were added 1.30 g of N, N-diethyl-N-methylethylenediamine and the solution was stirred at room temperature for one hour. The precipitate was filtered and suspended in 50 ml of water. The suspension was made alkaline with potassium carbonate, and extrated with ethyl acetate. The extract was washed with water, dried, and then evaporated to give 3.66 g of yellow oil.

IR spectrum ν (film)cm^{-1}:

1640 ($-CON<$, $>C=O$)

According to a conventional manner, the compound was changed to hydrochloride and fumarate.

hydrochloride: colorless plates (from ethanol) m.p. 221.5 to 222°C.

Elemental analysis for $C_{24}H_{28}N_2O_3 \cdot HCl$

	C	H	N
Calcd. (%)	67.20	6.81	6.53
Found (%)	67.09	6.88	6.35

fumarate: colorless plates (from ethanol), m.p. 165.5 to 167.5°C.

Elemental analysis for $C_{24}H_{28}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd. (%)	66.13	6.34	5.51
Found (%)	65.90	6.46	5.43

Example 8

N-[2-(N', N'-Diethylamino)ethyl]-N-methylflavone-8-carbox - amide:

To a solution of methylflavone-8-carboxylic acid chloride (prepared from 2.00 g of flavone-8-carboxylic acid and 1.1 ml of trionyl chloride) in 50 ml of benzene were added 0.88 g of N, N-diethyl-N-methylethlenediamine and the mixture was stirred at room temperature for 1.5 hours. The

reaction mixture was extracted with aqueous HCl solution. The water layer was made alkaline with potassium carbonate, and extracted with ethyl acetate. The extract was washed with water, dried, and then evaporated to give 2.32 g of a reddish oil.

IR spectrum ν (film)cm^{-1}:

1650 ($-CON<$, $>C=O$)

According to a conventional manner, the compound was changed to hydrochloride, which was recrystallized from ethanol - ether as give yellowish brown needles, m.p. 200.5 to 202°C.

Elemental analysis for $C_{23}H_{26}N_2O_3$. HCl

	C	H	N
Calcd. (%)	66.58	6.56	6.75
Found (%)	66.40	6.80	6.69

Example 9

N-[2-(N',N'-diethylamino)ethyl]-N-methyl-3-ethylflavone-8-carbox amide:

The mixture of 3-ethylflavone-8-carboxylic acid chloride (prepared from 3.00 g of 3-ethylflavone-8-carboxylic acid and 1.49 ml of thionyl chloride) and 1.19 g of N',N'-diethyl-N-methylethylenediamine were treated by the

same manner as that mentioned in Example 8 to give 3.69 g of reddish brown liquid.

IR spectrum ν (film)cm^{-1}

1640 (-CON<, >C=O)

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as colorless plates, m.p. 186 - 188.5°C.

Elemental analysis for $C_{25}H_{30}N_2O_3 \cdot C_4H_4O_4$

		C	H	N
Calcd.	(%)	66.65	6.56	5.36
Found	(%)	66.49	6.69	5.34

Example 10

N-[2-(N', N'-dimethylamino) ethyl]-N-methyl-3-methylflavone-8-carbox amide:

To a solution of 3.00 g of 3-methylflavone-8-carboxylic acid chloride in 60 ml of benzene were added 0.92 g of N, N-dimethyl-N-methylethylenediamine and the solution was stirred at room temperature for one hour. The precipitate was filtered, and filtrate was extracted with aquious HCl solution. To this water layer the obtained precipitate was added and the solution was made alkaline with potassium carbonate and extrated with chloroform. The extract was washed with water, dried, and then evaporated.

To the residue, isopropyl ether was added. The precipitate was filtrated to give 2.83 g of colorless crystals, m.p. 94 - 102°C.

IR spectrum ν (KBr)cm^{-1}:

1650, 1630 (-CON<, >C=O)

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol to give the colorless plates, m.p. 214.5 to 216°C.

Elemental analysis for $C_{22}H_{24}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd. (%)	64.99	5.87	5.83
Found (%)	64.81	5.86	5.59

Example 11

N-[2-(N', N'-diethylamino) ethyl]-N-ethyl-3-methylflavone-8-carboxamide:

To a solution of 3.00 g of 3-methylflavone-8-carboxylic acid chloride in 65 ml of benzene were added 1.30 g of N, N-diethyl-N-ethylethylenediamine and the mixture was stirred at room temperature for one hour, and the precipitate was filtered. The filtrate was extracted with aqueous HCl solution. The water layer and the obtained precipitate were

made alkaline with potassium carbonate and extrated with ethyl acetate. The ethyl acetate layer was washed with water, dried, and then evaporated to give 3.65 g of yellow liquid.

IR spectrum ν (film)cm^{-1}:

1640 ($-CON<$, $>C=O$)

According to a conventional manner, the compound was changed to hydrochloride and fumarate.

hydrochloride: colorless plates (from ethanol and ether), m.p. 185 to 187°C.

Elemental analysis for $C_{25}H_{31}N_2O_3 \cdot HCl.-H_2O$

	C	H	N
Calcd. (%)	67.10	7.09	6.26
Found (%)	67.11	7.20	6.02

fumarate: colorless plates (from ethanol), m.p. 172 to 175.5°C.

Elemental analysis for $C_{25}H_{30}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd. (%)	66.65	6.56	5.36
Found (%)	66.73	6.63	5.36

Example 12

N-[3-(piperidine-1-yl)propyl]-3-methylflavone-8-carbox amine:

To a solution of 1.51 g of 3-methylflavone-8-carboxylic acid chloride in 60 ml of benzene were added 0.65 g of N-(3-aminopropyl) piperidine and the solution was refluxed for 10 minutes. After cooling, the precipitate was filtrated and suspended in water. The suspension was made alkaline with potassium carbonate, and extrated with ethyl acetate. The ethylacetate layer was washed with water, dried, and the solvent was removed. To the residue ether was added. The precipitate was filtrated to give 0.78 g of colorless crystals, which were recrystallized from isoproyl ether, as colorless needles, m.p. 116.5 - 117.5°C.

According to a conventional manner, the compound was changed to hydrochloride, which was recrystallized from a mixture of ethanol and ether as colorless plates, m.p. 201 to 204°C.

Elemental analysis for $C_{25}H_{28}N_2O_3 \cdot HCL$

	C	H	N
Calcd. (%)	68.09	6.63	6.35
Found (%)	67.92	6.81	6.21

Example 13

N-[2-(piperidine-1-yl) ethyl]flavone-8-carbox amide:

To a solution of 3.49 g of flavone-8-carboxylic acid chloride in 80 ml of benzene were added 1.41 g of N-(2-aminoethyl) piperidine and the solution was stirred at room temperature for 1.5 hour. The precipitate was filtered and added to the mixture of ethyl acetate and aqueous HCl solution, and stirred. The water layer was made alkaline with potassium carbonate, and extrated with ethyl acetate. The ethyl acetate layer was washed with water, dried, and the solvent was removed. To the residue, ether was added. The precipitate was filtrated to give 2.17 g of colorless crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 162 - 165°C.

Elemental analysis for $C_{23}H_{24}N_2O_3 \cdot 1/2H_2O$

	C	H	N
Calcd. (%)	71.67	6.54	7.27
Found (%)	71.47	6.67	7.03

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as pale yellow needles, m.p. 109.5 to 211°C.

Elemental analysis for $C_{23}H_{24}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd. (%)	65.84	5.73	5.69
Found (%)	65.88	5.72	5.51

Example 14

N-[2-(piperidine-1-yl)ethyl]-3-methylflavone-8-carbox amide:

a) To a solution of 3.30 g of 3 -methylflavone-8-carboxyic acid chloride in 90 ml of benzene were added 1.27 g of N-(2-aminoethyl) piperidine and the mixture was stirred at room temperature for 40 minutes. The precipitate was filtrated and filtrate was stirred with aqueous HCl solution, and the precipitate was filtrated. The precipitate was suspended in water together with the former obtained precipitate and the supension was made alkaline with potassium carbonate and extracted with chlorofom. The chloroform layer was washed with water, dried, and the solvent was evaporated. To the residue ethyl acetate was added and the precipitate was filtrated to give 2.94 g of colorless crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 163 - 166°C.

Elemental analysis for $C_{24}H_{26}N_2O_3$

		C	H	N
Calcd.	(%)	73.82	6.71	7.17
Found	(%)	73.67	6.76	7.05

According to a conventioanl manner, the compound was changed to hydrochloride and fumarate.

hydrochloride: the colorless needles (from the mixture of ethanol and ether), m.p. 188 - 190°C.

Elemental analysis for $C_{24}H_{26}N_2O_3 \cdot HCl$

		C	H	N
Calcd.	(%)	67.52	6.37	6.56
Found	(%)	67.36	6.44	6.33

fumarate: colorless needles (from acetone), m.p. 139 - 142°C

Elemental analysis for $C_{24}H_{26}N_2O_3 \cdot C_4H_4O_4$

		C	H	N
Calcd.	(%)	66.39	5.97	5.53
Found	(%)	66.43	6.00	5.45

b) To a solution of 4.00 g of N-(2-aminoethyl)-piperidine in 40 ml of pyridine were added the solution of 1.36 ml of phosphous trichloride in 10 ml of pyridine under ice-cooling and the solution was stirred for 50 minutes at room temperature.

To the obtained solution were added 4.37 g of 3-methylflavone-8-carboxylic acid and the mixture was stirred at the bath temperature of 100°C for 2.5 hours. The solvent was evaporated and the residue was dissolved in aqueous HCl

solution and washed with ethyl acetate. The precipitate and the water layer were made alkaline with potassium carbonate and ectracted with chloroform. The chloroform layer was washed with water, dried, and the solvent was evaporated. To the residue was added isopropyl ether and the precipitate was filtered and recrystallized from ethyl acetate to give 2.80 g of colorless needles, m.p. 163 - 166°C. This compound was identical with the product obtained in Example 14-a) in NMR IR spectra, and mixed m.p..

Example 15

N-[2-(piperiden-1-yl) ethyl]-3-ethylflavone-8-carbox amide:

To a solution of 3-ethylflavone-8-carboxylic acid chloride (prepared from 3.00 g of 3-ethylflavone-8-carboxylic acid and 2.43 g of thionyl chloride) in 60 ml of benzene were added 1.18 g of N-(2-aminoethyl) piperidine and the solution was stirred at room temperature for 30 minutes. The reaction mixture was treated by the same manner as that described in Example 10 to give 3.44 g of colorless crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 166 - 167°C.

Elemental analysis for $C_{25}H_{28}N_2O_3$

	C	H	N
Calcd. (%)	74.23	6.98	6.93
Found (%)	74.05	7.15	6.78

According to a conventional manner the compound, was changed to hydrochloride, which was recrystallized from ethanol, as colorless plates, m.p. 200 - 202°C.

Elemental analysis for $C_{25}H_{28}N_2O_3 \cdot HCl$

	C	H	N
Calcd. (%)	68.09	6.63	6.35
Found (%)	67.89	6.61	6.26

Example 16

N-[2-(pyrrolidin-1-yl) ethyl]-3-methylflavone-8-caboxamide:

To a solution of 3-methylflavone-8-caboxylic acid chloide (prepared from 3.00 g of 3-methylflavone-8-carboxylic acid and 3.40 g of thionyl chloride) in 80 ml of benzene were added 1.04 g of N-(2-aminoethyl)pyrrolidine and the solution was refluxed for 10 minutes. After cooling to the reaction mixture aqueous HCl solution was added.The precipitate and water layer was made alkaline with potassium carbonate and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. To the sesidue was added ether and the precipitate was filtrated to give 2.80 g of colorless crystals, m.p. 179.5 - 181.5°C.

According to a conventional manner, the compound was changed to hydrochloride and fumarate.

hydrochloride: colorless needles (from mixture of ethanol and acetone), m.p. 108.5 - 111.5°C.

Elemental analysis for $C_{23}H_{24}N_2O_3 \cdot HCl \cdot H_2O$

	C	H	N
Calcd. (%)	64.11	6.32	6.50
Found (%)	64.18	6.39	6.28

fumarate: colorless prisms (from ethanol) m.p. 163 - 165°C.

Elemental analysis for $C_{23}H_{24}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	65.84	5.73	5.69
Found (%)	65.92	5.80	5.63

Example 17

N-[2-(morphoin-4-yl) ethyl]-3-methylflavone-8-carboxamide:

The same procedure as that described for Example 14 has been performed by using a solution of 3.00 g of 3-methylflavone-8-carboxylic acid chloride in 80 ml of benzene and 1.18 g of N-(2-aminoethyl) morpholine to give 2.99 g of colorless crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 198 - 201.5°C.

Elemental analysis for $C_{23}H_{24}N_2O_4 \cdot 1/4H_2O$

	C	H	N
Calcd. (%)	69.59	6.22	7.06
Found (%)	69.82	6.05	7.05

According to a conventional manner the compound was changed to hydrochloride, which was recrystallized from methanol as colorless needles, m.p. 210 - 212.5°C.

Elemental analysis for $C_{23}H_{24}N_2O_4 \cdot HCl$

	C	H	N
Calcd. (%)	64.41	5.87	6.53
Found (%)	64.23	5.88	6.36

Example 18

N-[3-(pyrrolidin-1-yl) propyl]flavone-8-carboxamide:

To a solution of 2.34 g of flavone-8-carboxylic acid chloride in 60 ml of benzene were added 0.95 g of N-(3-aminonpropyl) pyrrolidine and the solution was stirred at room temperature for 30 minutes. The reaction mixture was treated by the same manner as that described for Example 13, to give 1.48 g of pale brown crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 166 - 169.5°C.

Elemental analysis for $C_{23}H_{24}N_2O_3 \cdot 1/2H_2O$

	C	H	N
Calcd. (%)	71.67	6.54	7.27
Found (%)	72.06	6.47	7.19

According to a conventional manner the compound was changed to fumarate, which was recrystallized from a mixture of ethanol and acetone as colorless needles, m.p. 141.5 to 147°C.

Elemental analysis for $C_{23}H_{24}N_2O_3 \cdot C_4H_4O_4 \cdot 1/2H_2O$

	C	H	N
Calcd. (%)	64.66	5.83	5.59
Found (%)	64.53	5.87	5.54

Example 19

N-[3-(morphoin-4-yl) propyl]-3-methylflavone-8-carboxamide:

The same procedure as that described for Example 10 has been performed by using a solution of 3.00 g of 3-methylflavone-8-carboxylic acid chloride in 60 ml of benzene and 1.30 g of N-(3-aminopropyl) morpholine to give 2.82 g of colorless crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 161.5 - 162°C.

Elemental analysis for $C_{24}H_{26}N_2O_4$

	C	H	N
Calcd. (%)	70.92	6.45	6.89
Found (%)	70.72	6.33	6.86

According to a conventional manner, the compound was changed to hydrochloride, which was recrystallized from methanol as colorless needles, m.p. 217 - 220°C.

Elemental analysis for $C_{24}H_{26}N_2O_4 \cdot HCl$

	C	H	N
Calcd. (%)	65.08	6.14	6.32
Found (%)	64.96	6.17	6.31

Example 20

N-(1-Ethylpiperidin-3-yl)-3-methylflavone-8-carboxamide:

To a solution of 3.00 g of 3-methylfavone-8-carboxylic acid chloride in 60 ml of benzene were added 1.16 g of 3-amino-1-ethylpiperidine and the solution was stirred at room temperature for 1 hour. The mixture was treated by the same manner as that mentioned for Example 1 to give 3.17 g of colorless crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 188 - 189.5°C.

Elemental analysis for $C_{24}H_{26}N_2O_3$

	C	H	N
Calcd.(%)	73.82	6.71	7.17
Found (%)	74.10	6.78	7.19

According to a conventional manner, the compound was changed to hydrochloride and fumarate

hydrochloride: colorless needles (from acetone),

m.p. 141.5 - 144°C

Elemental analysis for $C_{24}H_{26}N_2O_3.HCl \cdot 3/2\ H_2O$

	C	H	N
Calcd.(%)	63.50	6.66	6.17
Found (%)	63.68	6.41	6.07

fumarate: colorless needles (from methanol),

m.p.212.5 - 215 (decomp.)

Elemental analysis for $C_{24}H_{26}N_2O_3.C_4H_4O_4$

	C	H	N
Calcd.(%)	66.39	5.97	5.53
Found (%)	66.35	5.96	5.46

Example 21

N-[(1-Ethylpyrrolidin-2-yl) methyl]-3-methylflavone-8-caboxamide;

To a solution of 3-methylflavone-8-caboxylic acid chloide (prepared from 4.00 g of 3-methylflavone-8-carboxylic

acid and 3.40 g of thionyl chloride) in 90 ml of benzene were added 1.66 g of 2-aminomethyl-1-ethylpyrrolidine and the solution refluxed for 1.5 hours. The reaction mixture was treated by the same manner as that mentioned for Example 16, to give 4.25 g of colorless crystals, which was recrystallized from isopropyl ether as colorless needles, m.p. 116.5 - 118°C.

Elemental analysis for $C_{24}H_{26}N_2O_3$

	C	H	N
Calcd.(%)	73.82	6.71	7.17
Found (%)	73.51	6.73	6.98

According to a conventional manner, the compound was changed to hychochloride and fumarate.

hydrochloride: colorless needles (from acetone),m.p. 115.5 - 117°C

Elemental analysis for $C_{24}H_{26}N_2O_3 \cdot HCl \cdot 5/4H_2O$

	C	H	N
Calcd.(%)	64.14	6.62	6.23
Found (%)	64.23	6.68	6.08

fumarate: pale brown plates (from ethanol), m.p. 181.5 - 183.5°C

Elemental analysis for $C_{24}H_{26}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Found (%)	66.37	6.16	5.43
Calcd.(%)	66.39	5.97	5.53

Example 22

N-[2-(1-Methylpyrrolidin-2-yl) ethyl]-3-methylflavone-8-carboxamide:

Using 3.00 g of 3-methylflavone-8-carboxylic acid chloride in 50 ml of benzene and 1.16 g of 2-(2-aminoethyl)-1-methyl pyrrolidine, the same reaction as that mentioned for Example 10 was performed to give 2.87 g of pale yellow crystals, which were recrystallized from ethyl acetate as pale yellow needles, m.p. 147 - 150.5°C.

Elemental analysis for $C_{24}H_{26}N_2O_3 \cdot 1/4\ H_2O$

	C	H	N
Calcd.(%)	72.98	6.76	7.09
Found (%)	72.99	6.61	6.90

According to a conventional manner, the conpound was changed to fumarate, which was recrystallized from ethanol as pale yellow plates, m.p. 175 - 177.5°C.

Elemental analysis for $C_{24}H_{26}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	66.39	5.97	5.53
Found (%)	66.27	5.59	5.55

Example 23

N-[2-(1-Methylpyrrolidine-2-yl) ethyl]-3-ethylflavone-8-carboxamide:

Using a solution of 3-ethylflavone-8-carboxylic acid chloride (prepared from 3.00 g of 3-ethylflavone-8-carboxylic

acid and 2.43 g of thionyl chloride) in 60 ml of benzene and 1.18g of 2-(2-aminoethyl)-1-methylpyrrolidine, the same procedure was performed as that mentioned for Example 10 to give 2.70g of colorless crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 163 - 165°C.

Elemental analysis for $C_{25}H_{28}N_2O_3$

	C	H	N
Calcd.(%)	74.23	6.98	6.93
Found (%)	73.95	7.05	6.82

According to a conventional manner, the conpound was changed to fumarate, which was recrystallized from ethanol as colorless needles, m.p. 164 - 166°C.

Elemental analysis for $C_{25}H_{28}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	66.91	6.20	5.38
Found (%)	66.87	6.17	5.37

Example 24

N-[(2-Dimethylamino-1-methyl) ethyl]flavone-8-carboxamide:

To a solution of flavone-8-carboxylic acid chloride (prepared from 1.00 g of flavone-8-carboxylic acid and 0.90 g of thionyl chloride) in 30 ml of benzene were added 0.35 g of (2-dimethylamino-1-methyl) ethylamine and stirred at room temperature for 80 minutes. The reaction mixture was treated

by the same manner as that mentioned for Example 1, to give 1.00 g of reddish brown crystales, which were recrystallized from ethyl acetate as colorless needles, m.p.190.5 - 191.5°C.

Elemental analysis for $C_{21}H_{22}N_2O_3$

	C	H	N
Calcd.(%)	71.98	6.33	7.99
Found (%)	72.15	6.46	7.98

According to a conventional manner, the conpound was changed to fumarate, which was recrystallized from methanol as pale brown needles, m.p. 196.5 - 197.0°C.

Elemental analysis for $C_{21}H_{22}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	64.39	5.62	6.01
Found (%)	64.33	5.85	5.98

Example 25

N-[(2-Dimethylamino-1-methyl)ethyl]-3-methylflavone-8-carboxamide:

Using a solution of 2.50 g of 3-methylflavone-8-carboxylic acid chloride in 40 ml of benzene and 0.77 g of (2-dimethyl-amino-1-methyl) ethylamine, the same reaction as that mentioned for Example 1 was performed to give 2.29g of colorless crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 148 - 151°C.

Elemental analysis for $C_{22}H_{24}N_2O_3$

	C	H	N
Calcd.(%)	72.51	6.64	7.69
Found	72.75	6.82	7.69

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as colorless plates, m.p. 182 - 183°C.

Elemental analysis for $C_{22}H_{24}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	64.99	5.87	5.83
Found (%)	65.20	6.07	5.81

Example 26

N-[(2-Diethylamino-1-methyl)ethyl]-3-methylflavone-8-carboxamide:

The same procedure as that mentioned in Example 1 was performed in using a solution of 3-methylflavone-8-carboxylic acid chloride (prepared from 3.0 g of 3-methylflavone-8-carboxylic acid and 2.56 g of thionyl chloride) in 30 ml of benzene and 1.25 g of (2-diethylamino-1-methyl) ethylamine to give 3.17 g of colorless crystals, which were recrystallized from isopropyl ether as colorless needles, m.p. 127 - 128°C.

Elemental analysis for $C_{24}H_{28}N_2O_3$

	C	H	N
Calcd.(%)	73.44	7.19	7.14
Found (%)	73.49	7.16	7.07

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as colorless prisms, m.p. 149.5 - 151° C.

Elemental analysis for $C_{24}H_{28}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	66.13	6.34	5.51
Found (%)	65.97	6.36	5.49

Example 27

N-[(2-Diethylamino-1-methyl)ethyl] -3-ethylflavone-8-carboxamide:

Using a solution of 3-ethylflavone-8-carboxylic acid chloride (prepared from 2.0 g of 3-ethylflavone-8-carboxylic acid and 1.62 g of thionyl chloride) in 30 ml of benzene and 0.80 g of 2-(diethylamino-1-methyl) ethylamine, the same procedure as that described in Example 1 was performed to give 1.83 g of colorless crystals, which were recrystallized from isopropyl ether as colorless needles, m.p. 117.5 - 118°C.

Elemental analysis for $C_{25}H_{30}N_2O_3$

	C	H	N
Calcd.(%)	73.86	7.44	6.89
Found (%)	74.05	7.53	6.88

Example 28

N-(2-Diethylaminopropyl)-3-methylflavone-8-carboxamide:

To a solution of 1.50 g of 3-methylflavone-8-carboxylic acid chloride in 30 ml of benzene were added 0.59g of 2-diethylaminopropylamine and stirred for 50 minutes at room temperature. To the reaction mixture was added aqueous HCl solution and the mixture was shaked. The water layer and the precipitate were separated from the organic layer and was made alkaline with potassium carbonate, and extracted with chloroform. The extract was washed with water, dried and evaporated to give 0.70 g yellow liquid. According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as pale reddish plates, m.p. 156.5 - 158.5°C.

Elemental analysis for $C_{24}H_{28}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	66.13	6.34	5.51
Found (%)	66.28	6.42	5.52

Example 29

N-[2-(1-Piperidyl)propyl]-3-methylflavone-8-carboxamide:

a) To a solution of 3.40 g of 3-methylflavone-8-carboxylic acid chloride in 110 ml of benzene were added 1.46 g of 2- (1-piperidyl) propylamine and the mixture was refluxed for 1.5 hours. The reaction mixture was treated by

same manner as that described in Example 5 to give 3.39 g of colorless crystals, which were recrystallized from ethyl acetate as colorless needless, m.p. 106.5 - 108.5°C.

Elemental analysis for $C_{25}H_{28}N_2O_3$

	C	H	N
Calcd.(%)	74.23	6.98	6.93
Found (%)	74.32	6.95	6.86

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from a mixture of ethanol and acetone as colorless needles, m.p. 145 - 148° C.

Elemental analysis for $C_{25}H_{28}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	66.91	6.20	5.38
Found (%)	66.92	6.52	5.19

b) To a solution of 4.00 g of 3-methylflavone-8-carboxylic acid and 1.98 ml of triethylamine in 74 ml of anhydrous tetrahydrofuran was added a solution of 1.50 ml of ethyl chlorocarboxnate in 15 ml of anhydrous tetrahydrofuran added under ice-cooling and the mixture was stirred for 1 hour. To the mixture, a solution of 2.03 g 2-piperidino-propylamine in 20 ml of anhydrous tetrahydrofuran were added and the mixture was stirred for 1.5 hours under ice-cooling and further at room temperature for 16 hours. The reaction

mixture was treated by the same procedure as mentioned in Examples 3-b) to give 4.15 g of colorless crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 106.5 - 108.5°C.

The compound was identical with the product obtained in Example 29-a) in NMR and IR spectra, and mixed m.p..

Example 30

N-(2-Diethylaminoethyl)-3,3'-dimethylflavone-8-carboxamide:

To a solution of 3,3'-dimethylflavone-8-carboxylic acid chloride (prepared from 1.00 g of 3,3'-dimethylflavone-8-carboxylic acid and 0.50 ml of thionyl chloride) in 30 ml of benzene were added 0.36 g of N,N-diethyl-aminoethylenediamine and was stirred for 2 hours at room temperature. To the mixture was added aqueous HCl solution and the mixture was shaken. The water layer was separated, and made alkaline with potassium carbonate and extracted with chloroform. The extract was washed with water, dried, and evaporated. The residue was purified by column chromatography (adsorbent: alumina, eluted with chloroform) as 0.35 g of yellow crystals, m.p. 79.5 - 86°C.

Example 31

N-(3-Piperidinopropyl)-3,3'-dimethylflavone-8-carboxamide:

To a solution of 3,3'-dimethylflavone-8-carboxylic acid chloride (prepared from 1.00 g of 3,3'-dimethylflavone-8-carboxylic acid and 0.50 ml of thionyl chloride) in 30 ml of benzene were added 0.44 g of 3-piperidinopropylamine and the mixture was stirred for 2 hours at room temperature. To the mixture was added aqueous HCl solution and the mixture was shaken. The water layer was separated and made alkaline with potassium carbonate and extracted with chloroform. The extract was washed with water, dried, and evaporated, and to the residue was added isopropyl ether. The precipitate was filtered to give 0.80 g of reddish brown crystals, which were recrystallized from a mixture of acetone and water as colorless needles, m.p. 112 - 114°C.

Elemental analysis for $C_{26}H_{30}N_2O_3$

	C	H	N
Calcd.(%)	74.61	7.22	6.69
Found (%)	74.24	7.17	6.65

Example 32

N-(2-Diethylaminoethyl)-3,4'-dimethylflavone-8-carboxamide:

Using a solution of 3,4'-dimethylflavone-8-carboxylic acid chloride (prepared from 1.00 g of 3,4'-dimethylflavone-

8-carboxylic acid and 0.50 ml of thionyl chloride) in 30 ml of benzene and 0.36 g of N,N-diethylethylenediamine, the same procedure as that mentioned in Example 31 was performed to give 0.91 g of pale yellow crystals, m.p. 108 - 113.5°C.

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as colorless prisms, m.p. 150 - 151°C.

Elemental analysis for $C_{24}H_{28}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd. (%)	66.13	6.34	5.51
Found (%)	66.13	6.38	5.46

Example 33

N-[(2-Dimethylamino-1-methyl)ethyl]-3,4'-dimethylflavone-8-carboxamide:

The same procedure as that mentioned in Example 31 was performed in using 0.31 g of (2-dimethylamino-1-methyl)ethylamine and a solution of 3.4'-dimethylflavone-8-carboxylic acid chloride (prepared from 1.00 g of 3,4'-dimethylflavone-8-carboxylic acid and 0.50 ml of thionyl chloride) in 30 ml benzene to give 0.97 g of pale yellow crystals, which were recrystallized from ethyl acetate as pale brown needles, m.p. 155 - 156°C.

Elemental analysis for $C_{23}H_{26}N_2O_3$

	C	H	N
Calcd.(%)	72.99	6.92	7.40
Found (%)	72.92	6.77	7.40

According to a conventional manner, the compound was charged to fumarate, which was recrystalled from ethanol as colorless plates, m.p. 187.5 - 189.5°C.

Elemental analysis for $C_{23}H_{26}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	65.58	6.11	5.66
Found (%)	65.64	6.26	5.59

Example 34

N-(2-Diethylaminoethyl)-3'-methoxy-3-methylflavone-8-carboxamide:

The same procedure as that mentioned in Example 31 was performed in using 0.67 g of N,N-diethylethylenediamine and a solution of 3'-methoxy-3-methylflavone-8-carboxylic acid chloride (prepared from 2.00g of 3'-methoxy-3-methyl-flavone-8-carboxylic acid and 4.72 ml of thionyl chloride) in 60 ml of benzene to give 1.36 g of yellow crystals, which were recrystallized from a mixture of ethyl acetate and isopropyl ether as colorless needles, m.p. 90.5 - 91.5°C.

Elemental analysis for $C_{24}H_{28}N_2O_3$

	C	H	N
Calcd.(%)	70.57	6.91	6.86
Found (%)	70.34	6.71	6.72

Example 35

N-(2-Piperidinopropyl)-3'-methoxy-3-methylflavone-8-carboxamide:

The same procedure as that mentioned in Example 31 was performed in using 0.41 g of 2-piperidinopropylamine and a solution of 3'-methoxy-3-methylflavone-8-carboxylic acid chloride (prepared from 1.00 g 3'-methoxy-3-methylfavone-8-carboxylic acid and 1.88 ml of thionyl chloride) in 30 ml of benzene to give 0.61 g of pale yellow crystals, which were recrystallized from a mixture of ethyl acetate and isopropyl ether as colorless needles m.p. 95 - 97°C.

Elemental analysis for $C_{26}H_{30}N_2O_4$

	C	H	N
Calcd.(%)	71.87	6.96	6.45
Found (%)	71.80	6.91	6.47

Example 36

N-(2-Diethylaminoethyl)-4'-methoxy-3-methylflavone-8-carboxamido:

a) The same procedure as that mentioned in Example 31 was performed in using 0.34 g of N,N-diethylethylenediamine and a solution of 4'-methoxy-3-methylflavone-8-carboxylic acid chloride (prepared from 1.00 g of 4'-methoxy-3-methyl-flavone-8-carboxylic acid and 0.71 ml of thionyl chloride) in 50 ml of benzene to give 1.05 g of pale yellow crystals, which were recrystallized from ethyl acetate as colorless

needles m.p. 125.5 - 127°C.

Elemental analysis for $C_{24}H_{28}N_2O_4$

	C	H	N
Calcd.(%)	70.57	6.91	6.86
Found (%)	70.42	7.04	6.85

b) To a solution of 6.00 g of 4'-methoxy-3-methylflavone- 8-carboxylic acid and 2.70 ml of triethylamine in 70 ml of anhydrous tetrahydrofuran was added a solution of 2.03 ml of ethyl chlorocarbonate in 10 ml of anhydrous tetrahydrofuran and the mixture was stirred for 1 hour under ice-cooling. To the reaction mixture was added a solution of 2.25 g of N,N-diethylethylenediamine in 10 ml of anhydrous tetrahydrofuran and the mixture was stirred for 1.5 hours under ice-cooling and further 16 hours at room temperature. The reaction mixture was treated by the same procedure as that mentioned in Example 3-b), to give 3.55 g of pale yellow crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 125.5 - 127°C. This compound was identical with the product obtained in Example 36-a) in NMR and IR spectra, and mixed m.p..

Example 37

N-(2-Diethylaminoethyl)-3'-chloro-3-methylflavone-8-carboxamide:

To a solution of 3'-chloro-3-methylflavone-8-carboxylic acid chloride (prepared from 1.00 g of 3'-chloro-3-methylflavone-8-carboxylic acid and 0.46 ml of thionyl chloride) in 40 ml of benzene were added 0.33 g of N,N-diethylethylenediamine and the solution was stirred for 80 minutes at room temperature. To the reaction mixture was added aquesous HCl solution and shaken. The water layer was separated and made alkaline with potassium carbonate and extracted with chloroform. The extract was washed with water, dried, and evaporated. The residue was purified by column chromatography (adsorbent: silica gel, eluted with chloroform and chloroform containing 1% of methanol) to give 0.39 g of yellow crystals, which were recrystallized from isopropyl ether as colorless plates, m.p. 116 - 117°C.

Elemental analysis for $C_{23}H_{25}ClN_2O_3$

	C	H	N
Calcd.(%)	66.90	6.10	6.78
Found (%)	66.67	6.18	6.56

Example 38

N-(2-Diethylaminoethyl)-3'-methylflavone-8-carboxamide:

The same procedure as that mentioned in Example 31 was

performed in using 0.37 g of N,N-diethylethylenediamine and a solution of 3'-methylflavone-8-carboxylic acid chloride (prepared from 1.00 g of 3'-methylflavone-8-carboxylic acid and 0.52 ml of thionyl chloride) in 40 ml of benzene to give 0.9 g of pale yellow crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 160.5 - 162.5°C.

Elemental analysis for $C_{23}H_{26}N_2O_3$

	C	H	N
Calcd.(%)	72.99	6.92	7.40
Found (%)	72.59	6.85	7.28

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as colorless needles, m.p. 167 - 168.5°C.

Elemental analysis for $C_{23}H_{26}N_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	65.58	6.11	5.66
Found (%)	65.88	6.16	5.73

Example 39

N-[(2-Dimethylamino-1-methyl)ethyl]-3'-methylflavone-8-carboxamide:

The same procedure as that mentioned in Example 31 was performed in using 0.33 g of (2-dimethylamino-1-methyl)-

ethylamine and a solution of 3'-methylflavone-8-carboxylic acid chloride (prepared from 1.00 g of 3'-methylflavone-8-carboxylic acid and 0.52 ml of thionyl chloride) in 40 ml of benzene to give 1.01 g of pale yellow crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 156 - 157.5°C.

Elemental analysis for $C_{22}H_{24}N_2O_3$

	C	H	N
Calcd.(%)	72.51	6.64	7.69
Found (%)	72.61	6.64	7.69

According to a conventional manner, the compoound was changed to fumarate, which was recrystallized from methanol to give colorless needles, m.p. 185 - 187.5°C.

Elemental analysis for $C_{22}H_{24}N_2O_3 \cdot C_4H_4O_4 \cdot 1/4H_2O$

	C	H	N
Calcd.(%)	64.39	5.92	5.78
Found (%)	64.28	5.92	5.60

Example 40

N-(2-Diethylaminoethyl)-4'-methylflavone-8-carboxamide:

The same procedure as that mentioned in Example 31 was performed in using 0.37 g of N,N-diethylethylenediamine and a solution of 4'-methylflavone-8-carboxylic acid chloride (prepared from 1.00 g of 4'-methylflavone-8-carboxylic acid and 0.60 ml of thionyl chloride) in 30 ml of benzene to give

0.96 g of brown crystals.

Example 41

N-(2-Diethylaminoethyl)-3'-methoxyflavone-8-carboxamide:

The same procedure as that mentioned in Example 31 was performed in using 0.35 g of N,N-diethylethylenediamine and a solution of 3'-methoxyflavone-8-carboxylic acid chloride (prepared from 1.00 g of 3'-methoxyflavone-8- carboxylic acid and 0.49 ml of thionyl chloride) in 30 ml of benzene to give 0.95 g of pale brown crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 151.5 - 152.5°C.

Elemental analysis for $C_{23}H_{26}N_2O_4$

	C	H	N
Calcd.(%)	70.03	6.64	7.10
Found (%)	70.03	6.63	6.96

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as colorless needles, m.p. 172 - 173°C.

Elemental analysis for $C_{23}H_{26}N_2O_4 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	63.52	5.92	5.49
Found (%)	63.42	6.20	5.45

Example 42

N-(2-Piperidinopropyl)-3'-methoxyflavone-8-carboxamide:

The same procedure as that mentioned in Example 31 was performed in using 0.43 g of 2-piperidinopropylamine and a solution of 3'-methoxyflavone-8-carboxylic acid chloride (prepared from 3'-methoxyflavone-8-carboxylic acid and 0.49ml of thionyl chloride) in 30 ml of benzene to give 1.09 g of pale yellow crystals, which were recrystallized from ethanol as pale brown plates, m.p. 163 - 164°C.

Elemental analysis for $C_{25}H_{28}N_2O_4$

	C	H	N
Calcd.(%)	71.41	6.71	6.66
Found (%)	71.36	6.82	6.58

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from methanol as pale brown needles, m.p. 175 - 176.5°C (decomp.).

Elemental analysis for $C_{25}H_{28}N_2O_4 \cdot C_4H_4O_4 \cdot 1/2H_2O$

	C	H	N
Calcd.(%)	63.84	6.10	5.13
Found (%)	63.94	6.02	5.10

Example 43

N-(2-Diethylaminoethyl)-4'-methoxyflavone-8-carboxamide:

The same procedure as that mentioned in Example 31 was performed in using 0.35 g of N,N-diethylethylenediamine and a

solution of 4'-methoxyflavone-8-carboxylic acid chloride (prepared from 1.00 g of 4'-methoxyflavone-8-carboxylic acid and 0.74 ml of thionyl chloride) in 30 ml of benzene to give 0.91 g of pale brown crystals, m.p. 156.5 - 158.5°C.

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as colorless plates, m.p. 151 - 154°C.

Elemental analysis for $C_{23}H_{26}N_2O_4 \cdot C_4H_4O_4 \cdot H_2O$

	C	H	N
Calcd.(%)	61.36	6.10	5.30
Found (%)	61.26	5.89	5.37

Example 44

N-(2-Piperidinopropyl)-4'-methoxyflavone-8-carboxamide:

To a suspension of 4'-methoxyflavone-8-carboxylic acid chloride (prepared from 3.00 g of 4'-methoxyflavone-8-carboxylic acid and 1.48 ml of thionyl chloride) in 60 ml of benzene were added 1.30 g of 2-piperidinopropylamine and the mixture was stirred for 40 minutes at room temperature and refluxed for 1 hour. The reaction mixture was treated by the same manner as that described in Example 5 to give 1.80 g of pale brown crystals, which were recrystallized from ethanol as colorless needles, m.p. 171.5 - 174.5°C.

Elemental analysis for $C_{25}H_{28}N_2O_4$

	C	H	N
Calcd.(%)	71.41	6.71	6.66
Found (%)	71.34	6.74	6.50

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from méthanol as colorless needles, m.p. 216 - 219°C (decomp.).

Elemental analysis for $C_{25}H_{28}N_2O_4 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	64.91	6.01	5.22
Found (%)	65.01	5.87	5.11

Example 45

N-(2-Diethylaminoethyl)-3'-chloroflavone-8-carboxamide:

The same procedure as that described in Example 31 was performed in using 0.35 g of N,N-diethylethylenediamine and a solution of 3'-chloroflavone-8-carboxylic acid chloride (prepared from 1.00 g of 3'-chloroflavone-8-carboxylic acid and 0.73 ml of thionyl chloride) in 30 ml of benzene to give 1.03 g of pale brown crystals. According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as colorless needles, m.p. 186 - 188°C.

Elemental analysis for $C_{22}H_{23}ClN_2O_3 \cdot C_4H_4O_4 \cdot 1/2H_2O$

	C	H	N
Calcd.(%)	59.60	5.39	5.35
Found (%)	59.58	5.48	5.37

Example 46

N-(3-Piperidinopropyl)-3'-chloroflavone-8-carboxamide:

The same procedure as that described in Example 31 was performed in employing 0.43 g of 3-piperidinopropylamine and 3'-chloroflavone-8-carboxylic acid chloride (prepared from 1.00 g of 3'-chloroflavone-8-carboxylic acid and 0.73 ml of thionyl chloride) in 30 ml of benzene to give 1.14 g of pale brown crystals.

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from a mixture of ethanol and ether as pale brown needles, m.p. 151.5 - 153.5°C.

Elemental analysis for $C_{24}H_{25}ClN_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	62.16	5.40	5.18
Found (%)	62.16	5.38	5.22

Example 47

N-(2-Diethylaminoethyl)-4'-chloroflavone-8-carboxamide:

The same procedure as that described in Example 31 was performed in employing 0.35 g of N,N-diethylethylenediamine and a solution of 4'-chloroflavone-8-carboxylic acid chloride (prepared from 1.00 g of 4'-chloroflavone-8-carboxylic acid and 0.73ml of thionyl chloride) in 40 ml of benzene to give 0.83g of pale brown crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 181.5 - 184°C.

Elemental analysis for $C_{22}H_{23}ClN_2O_3$

	C	H	N
Calcd.(%)	66.24	5.81	7.02
Found (%)	66.08	5.70	7.04

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from methanol as pale yellow needles, m.p. 174.5 - 176°C.

Elemental analysis for $C_{22}H_{23}ClN_2O_3 \cdot C_4H_4O_4 \cdot 1/2H_2O$

	C	H	N
Calcd.(%)	59.60	5.39	5.35
Found (%)	59.72	5.45	5.38

Example 48

N-[(2-Dimethylamino-1-methyl)ethyl]-4'-chloroflavone-8-carboxamide:

The same procedure as that described in Example 31 was

performed in employing 0.31 g of (2-dimethylamino-1-methyl)-ethylamine and a solution of 4'-chloroflavone-8-carboxylic acid chloride (prepared from 1.00 g of 4'-chloroflavone-8-carboxylic acid and 0.73 ml of thionyl chloride) in 40 ml of benzene to give 0.80 g of pale brown crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 215.5 - 217°C.

Elemental analysis for $C_{21}H_{21}ClN_2O_3$

	C	H	N
Calcd.(%)	65.54	5.50	7.28
Found (%)	65.19	5.54	7.17

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from methanol as pale yellow needles, m.p. 199.5 - 203°C.

Elemental analysis for $C_{21}H_{21}ClN_2O_3 \cdot C_4H_4O_4 \cdot H_2O$

	C	H	N
Calcd.(%)	57.86	5.24	5.40
Found (%)	57.59	5.23	5.40

Example 49

N-(2-Diethylaminoethyl)-4'-fluoroflavone-8-carboxamide:

The same procedure as that described in Example 31 was performed in employing 0.37 g of N,N-diethylethylenediamine and a solution of 4'-fluoroflavone-8-carboxylic acid chloride

(prepared from 1.00 g of 4'-fluoroflavone-8-carboxylic acid and 0.77 ml of thionyl chloride) in 30 ml of benzene to give 0.90 g of pale brown crystals, which were recrystallized from ethanol as pale yellow needles, m.p. 173.5 - 175°C.

Elemental analysis for $C_{22}H_{23}FN_2O_3$

	C	H	N
Calcd.(%)	69.09	6.06	7.33
Found (%)	69.13	5.79	7.33

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as pale brown needles, m.p. 181 - 183.5°C.

Elemental analysis for $C_{22}H_{23}FN_2O_3 \cdot C_4H_4O_4 \cdot 1/2H_2O$

	C	H	N
Calcd.(%)	61.53	5.56	5.52
Found (%)	61.33	5.90	5.21

Example 50

N-(2-Piperidinopropyl)-4'-fluoroflavone-8-carboxamide:

The same procedure as that described in Example 31 was performed in employing 0.45 g of 2-piperidinopropylamine and a solution of 4'-fluoroflavone-8-carboxylic acid chloride (prepared from 1.00 g of 4'-fluoroflavone-8-carboxylic acid and 0.77 ml of thionyl chloride) in 30 ml of benzene to give 0.9 g of pale brown crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 177.5 - 179.5°C.

Elemental analysis for $C_{24}H_{25}FN_2O_3$

	C	H	N
Calcd.(%)	70.57	6.17	6.86
Found (%)	70.47	6.19	6.89

According to a conventional manner, the compound was changed to fumarate, which was recrystallized from methanol as colorless needles, m.p. 233 - 236°C.

Elemental analysis for $C_{24}H_{25}FN_2O_3 \cdot C_4H_4O_4$

	C	H	N
Calcd.(%)	64.11	5.57	5.34
Found (%)	64.12	5.52	5.36

Example 51

N-(2-Diethylaminoethyl)-4'-nitroflavone-8-carboxamide:

The same procedure as that described in Example 31 was performed in employing 0.34 g of N,N-diethylethylenediamine and 4'-nitroflavone-8-carboxylic acid chloride (prepared from 1.00 g of 4'-nitroflavone-8-carboxylic acid and 1.40 ml of thionyl chloride) in 30 ml of benzene to give 0.78 g of yellow crystals, which were recrystallized from methanol as yellowish brown crystals, m.p. 207 - 209°C.

Elemental analysis for $C_{22}H_{23}N_3O_5$

	C	H	N
Calcd.(%)	64.54	5.66	10.26
Found (%)	64.50	5.40	10.06

Example 52

N-(3-Piperidinopropyl)-3'-chloro-3-methylflavone-8-carboxamide:

The same procedure as that described in Example 31 was performed in employing 0.41 g of 3-piperidinopropylamine and a solution of 3'-chloro-3-methylflavone-8-carboxylic acid chloride (prepared from 1.00 g of 3'-chloro-3-methylflavone-8-carboxylic acid and 1.39 ml of thionyl chloride) in 30 ml of benzene to give 1.19 g of pale brown crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 128 - 131°C.

Elemental analysis for $C_{25}H_{27}ClN_2O_3$

	C	H	N
Calcd.(%)	68.41	6.20	6.38
Found (%)	68.41	6.23	6.17

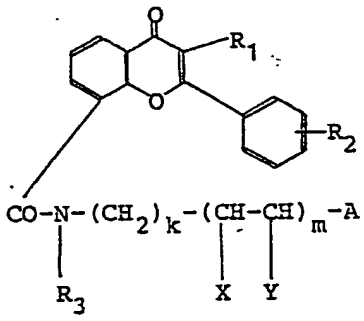
According to a conventional manner, the compound was changed to fumarate, which was recrystallized from ethanol as pale brown needles, m.p. 124 - 125.5°C.

Elemental analysis for $C_{25}H_{27}ClN_2O_3 \cdot C_4H_4O_4$

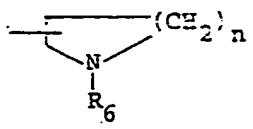
	C	H	N
Calcd.(%)	62.76	5.63	5.05
Found (%)	62.75	5.71	4.89

We claim:

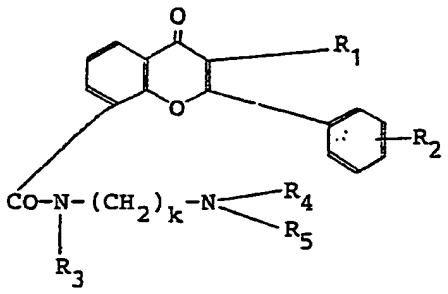
1. N-substituted flavone-8-carboxamides represented by the formula (I):

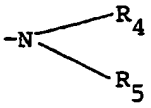


(I)

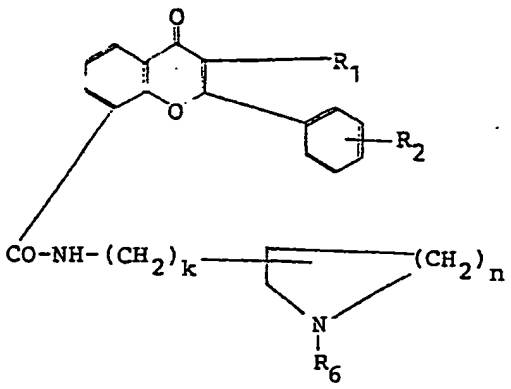
wherein R_1 represents a hydrogen atom, a methyl group or an ethyl group; R_2 represents a hydrogen atom, a lower alkyl group, a lower alkoxyl group, a halogen atom or a nitro group; R_3 represents a hydrogen atom or a lower alkyl group; k represents 0,1,2, or 3; m represents 0 or 1, X and Y, which must be different, represent a hydrogen atom or a methyl group; A represents an amino group having the  or  wherein, R_4 and R_5, which may be the same or different, represent a lower alkyl group or a cyclic amino group together with the nitrogen atom and with or without an oxygen atom; R_6 represents a lower alkyl group and n represents 2 or 3; and pharmaceutically acceptable acid addition salts thereof.

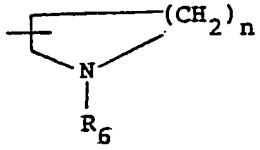
2. N-substituted flavone-8-carboxamides of claim 1.) represented by the formula



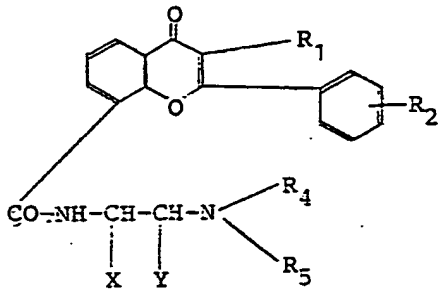
wherein R_1, R_2, R_3, and the group  having the same meanings as defined above and k means 2 or 3.

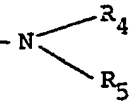
3. N-substituted flavone-8-carboxamides of claim 1.) represented by the formula



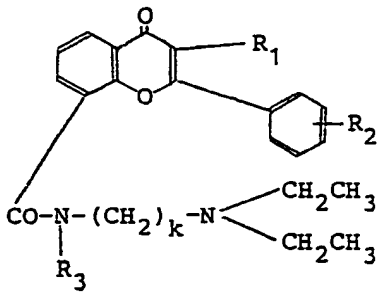
wherein R_1, R_2 and the group  having the same meaning as defined above and k means 0, 1 or 2.

4. N-substituted flavone-8-carboxamides of claim 1.) represented by the formula:



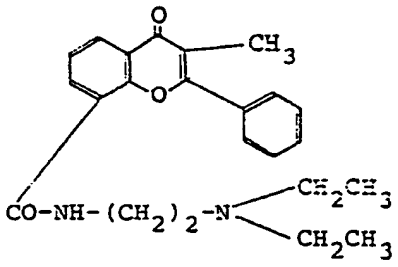
wherein R_1, R_2, X, Y, and the group  having the same meanings as defined above.

5. N-substituted flavone-8-carboxamides of claim 2.) represented by the formula:

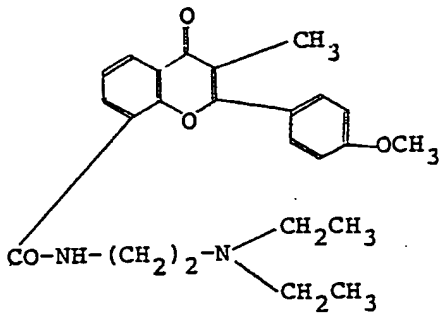


wherein R_1, R_2 and R_3 having the same meanings as defined above and k means 2 or 3.

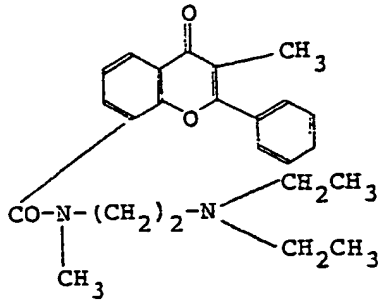
6. N-substituted flavone-8-carboxamides of claim 5.) represented by the formula



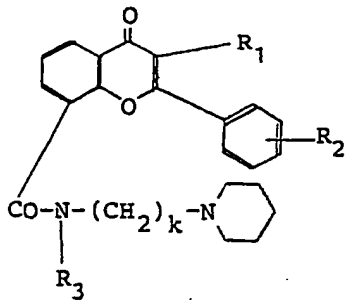
7. N-substituted flavone-8-carboxamides of claim 5.) represented by the formula:



8. N-substituted flavone-8-carboxamides of claim 5.)represented by the formula:

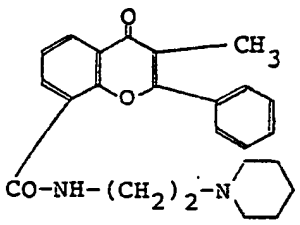


9. N-substituted flavone-8-carboxamides of claim 2.) represented by the formula:

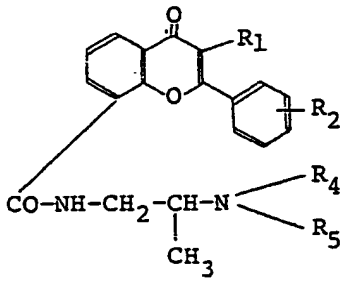


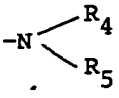
wherein R_1, R_2, R_3 having the same meanings as defined above and k means 2 or 3.

10. N-substituted flavone-8-carboxamides of claim 9.) represented by the formula:

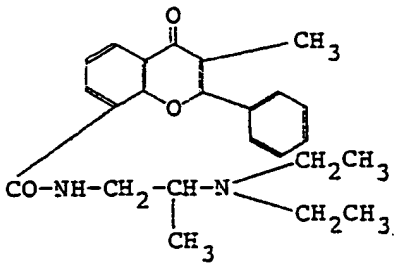


11. N-substituted flavone-8-carboxamides of claim 4.) represented by the formula:

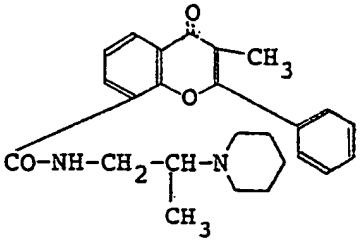


wherein R_1, R_2 and the group  having the same meanings as defined above.

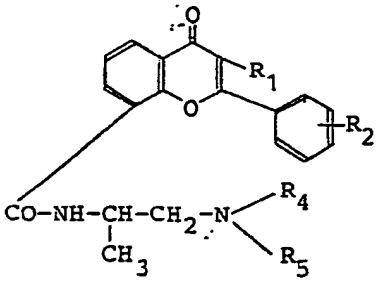
12. N-substituted flavone-8-carboxamides of claim 11.) represented by the formula:

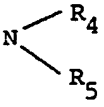


13. N-substituted flavone-8-carboxamides of claim 11.) represented by the formula:

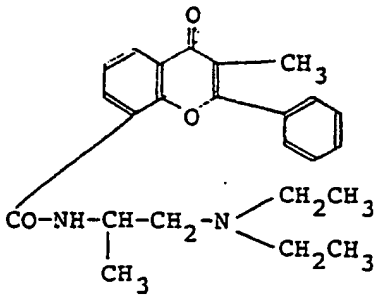


14. N-substituted flavone-8-carboxamides of claim 4.) represented by the formula:

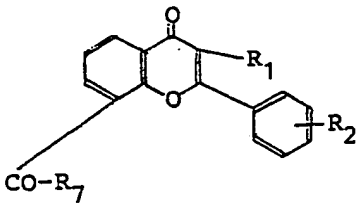


wherein R_1, R_2 and the group  having the same meanings as defined above.

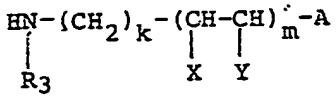
15. N-substituted flavone-8-carboxamides of claim 14.) represented by the formula:



16. A process for preparation of N-substituted flavon-8-carboxamides represented by the general formula I and pharmaceutically acceptable acid addition salts thereof characterized in that a flavone-8-carboxylic acid derivative represented by the formula

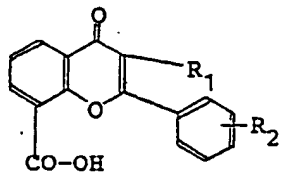


wherein R_1 and R_2 having the same meanings as defined above, and R_7 represents a hydroxyl group, a halogen atom, a group $-O-R_8$ or $-O-CO-O-R_9$ wherein R_8 and R_9 represents a lower alkyl group, with a diamine derivative represented by the formula:



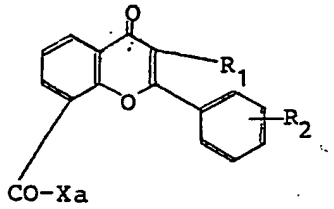
wherein R_3, X, Y, m and A having the same meanings as defined above and k means 0, 1, 2 or 3.

17. A process for preparation of claim 16.) wherein said flavone-8-carboxlic acid is a compound represented by the formula:



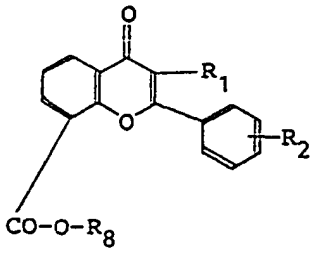
wherein R_1, R_2 having the same maenings as defined above.

18. A process for preparation of claim 16.), wherein said flavone-8-carboxylic acid is a compound represented by the formula:



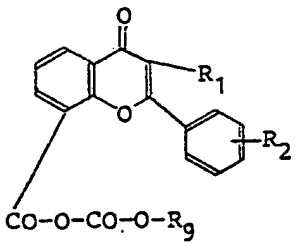
wherein R_1 and R_2 having the meanings defined above and Xa means a halogen atom.

19. A process for preparation of claim 16.) wherein said flavone-8-carboxlic acid derivative is a compound represented by the formula:



wherein R_1, R_2 and R_8 having the same meanings as defined above.

20. A process for preparation of claim 16.) characterized in that as flavone-8-carboxylic acid derivative a compound represented by the formula:



wherein R_1, R_2 and R_9 having the same meanings as defined above.

21. A pharmaceutical composition, suitable for use in treating the hinderances in micturition comprising a compound of claim 1.) in an amount effective for such purpose in asscciating which a pharmaceutically acceptable carrier.

22. A method for the treatment of a subject in read of elimination of the hinderance in micturition comprising the step of administering to a said subject an amount of a compound of claim 1.) for such purpose.

23.) A method of claim 22.) wherein the compound of claim 1.) is administered in associating with a pharmaceutically acceptable carrier.

0108986

European Patent Office

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which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number EP 83 11 0842

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
A	FR - A - 2 255 894 (C. ERBA) * Pages 1,14,15; claims pages 32-41 *	1,21	C 07 D 311/30 C 07 D 405/12 A 61 K 31/35

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

C 07 D 311/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-21

Claims searched incompletely:

Claims not searched: 22,23

Reason for the limitation of the search: Method for treatment of the human or animal body by surgery or therapy (see art. 52(4) of the European Patent Convention).

Place of search	Date of completion of the search	Examiner
The Hague	25-01-1984	FRANCOIS

CATEGORY OF CITED DOCUMENTS

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